FILE 'CAPLUS' ENTERED AT 10:12:25 ON 20 APR 2001

=> S PRODRUG;S DRUG;S INORGANIC;S GEL;S SOL(W)GEL

L1 6190 PRODRUG

L2 368800 DRUG

L3 59404 INORGANIC

L4 348025 GEL

347215 SOL
348025 GEL
L5 24739 SOL(W)GEL

=> S L1 AND L5

L6 0 L1 AND L5

=> S L1 AND L4

L7 66 L1 AND L4

=> S L7 AND L3

L8 0 L7 AND L3

=> D L7 1-66 TI

=> D L7 10,28,30,32,40-42,51 CBIB ABS

L7 ANSWER 10 OF 66 CAPLUS COPYRIGHT 2001 ACS
1999:68963 Document No. 130:290899 Treatment options for acute seizure care. Use of new formulations. Morton, Lawrence D.; Pellock, John M. (Division of Child Neurology, Departments of Neurology, Pediatrics, Pharmacy and Pharmaceutics, MCV Comprehensive Epilepsy Institute, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA, USA). CNS Drugs, 10(6), 405-416 (English) 1998. CODEN: CNDREF. ISSN: 1172-7047. Publisher: Adis International Ltd..

AB A review with 70 refs. The advent of new anticonvulsants, the resurgence of the ketogenic diet, and the currently available surgical techniques mean that practitioners have many options for long term prophylaxis of seizure recurrence. Unfortunately, breakthrough seizures still occur. In some situations, an addnl. dose of the patient's maintenance medication, or adjustment of the daily dose, is the most appropriate course of action for the management of such breakthroughs. However, in some situations, the patient may be unwilling or unable to cooperate and so oral administration of anticonvulsants is not possible. Until recently, only benzodiazepines, phenytoin and phenobarbital (phenobarbitone) have been available for parenteral administration; however, alternative treatment options have been developed: diazepam ***gel*** for rectal administration, fosphenytoin (a phenytoin ***prodrug***) and an i.v. formulation of valproic acid (sodium valproate). An i.v. formulation of diazepam has been long used for seizure treatment and has shown good efficacy. The ***gel*** formulation showed >60% efficacy for preventing seizures over 12 to 24 h in 2 controlled studies. No life-threatening adverse reactions were reported. Fosphenytoin is rapidly converted to phenytoin with a conversion half-life of 8 to 15 min following i.v. administration, and can be given in a variety of solns. It may also be administered i.m. Fosphenytoin infusion has not been assocd. with tissue necrosis and there have been fewer cardiac complications than are seen with i.v. infusion of phenytoin. I.v. valproic acid shows linear pharmacokinetics, and administration by this route has been demonstrated to maintain therapeutic concns. in patients and offers an alternative when patients cannot take the drug orally. I.v. valproic acid has been shown to be well tolerated.

L7 ANSWER 28 OF 66 CAPLUS COPYRIGHT 2001 ACS
1995:365088 Document No. 122:170028 Macromolecular prodrugs. IV.

Alginate-chitosan microspheres of PHEA-L-dopa adduct. Filipovic-Grcic, J.; Maysinger, D.; Zorc, B.; Jalsenjak, I. (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia). Int. J. Pharm., 116(1), 39-44 (English) 1995. CODEN: IJPHDE. ISSN: 0378-5173.

AB A polymeric ***prodrug*** .alpha.,.beta.-poly(N-hydroxyethyl)-DL-aspartamide-L-dopa adduct (PHEA-L-dopa) was microencapsulated in alginate-chitosan microspheres in order to achieve drug release from a complex reservoir device. The ***gel*** /matrix material of alginate-chitosan complex protects the adduct from hydrolysis by the surrounding medium. On the basis of a 103-fold difference between the drug released from microspheres as the adduct and that released in the unbound form, a model of the microencapsulated system was proposed.

L7 ANSWER 30 OF 66 CAPLUS COPYRIGHT 2001 ACS

1994:14729 Document No. 120:14729 Chemisorbates of p-hydroxybenzoic acid methyl ester on silica as a new type of ***prodrug*** . IV. Drug release from chemisorbates dispersed in lipophilic vehicles. Srcic, S.; Rupprecht, H.; Daca, J.; Smid-Korbar, J. (Fac. Nat. Sci. Technol., Univ. Ljubljana, Ljubljana, 61000, Slovenia). Int. J. Pharm., 99(1), 21-8 (English) 1993. CODEN: IJPHDE. ISSN: 0378-5173.

AB The hydrolysis of the chemisorbate of p-hydroxybenzoic acid Me ester (PHBAME) on porous silica (KG 100) incorporated in lipophilic vehicles such as liq. paraffin, synthetic oil Miglyol 818 and white petrolatum was examd. in dissoln. media at pH 2 and 7.4, resp. Chemisorbed PHBAME on KG 100 is released more rapidly in alk. than in acidic dissoln. fluids. Dispersions of the PHBAME-KG 100 chemisorbate in lipophilic vehicles modify the hydrolysis significantly. Drug release from chemisorbate dispersed in lipophilic vehicles may be controlled by the polarity of the vehicles. However, the viscosity of the vehicle, and not the polarity, exerts the strongest influence on the drug release.

L7 ANSWER 32 OF 66 CAPLUS COPYRIGHT 2001 ACS

1993:455877 Document No. 119:55877 Drug delivery system using biodegradable carrier. Tokura, S.; Miura, Y.; Kaneda, Y.; Uraki, Y. (Fac. Sci., Hokkaido Univ., Sapporo, 060, Japan). ACS Symp. Ser., 520(Polymeric Delivery Systems), 351-61 (English) 1993. CODEN: ACSMC8. ISSN: 0097-6156.

AB 6-O-Carboxymethyl chitin (CM-chitin), one of the biodegradable chitin derivs., shows several specificities such as chelating ability with calcium ion, specific adsorption of benzyl group following to the calcium chelation, and ***gel*** formation with trivalent iron ion. A ***prodrug*** was released slowly into blood following the s.c. injection of polymeric drugs, in which the ***prodrug*** was either pendanted through a covalent bond to CM-chitin or entrapped within CM-chitin matrix in the presence of Fe3+. The ***prodrug*** was then hydrolyzed, to become the active form, by enzymes in the blood.

L7 ANSWER 40 OF 66 CAPLUS COPYRIGHT 2001 ACS

1991:663334 Document No. 115:263334 Mixed micelles as a proliposomal, lymphotropic drug carrier. Supersaxo, Andreas; Hein, Wayne R.; Steffen, Hans (F. Hoffmann-La Roche Ltd., Basel, CH-4002, Switz.). Pharm. Res., 8(10), 1286-91 (English) 1991. CODEN: PHREEB. ISSN: 0724-8741.

AB Four lipophilic, low-mol.-wt. drugs solubilized in phosphatidylcholine-bile salt mixed micelles were injected s.c. into the hind legs of sheep and their cumulative recoveries in lymph draining from the site of application were detd. Surprisingly, the cumulative recoveries (percentage of dose) varied between <1 and 60%. There is a correlation between the lipophilicity of the drug (log P octanol/water - Rm.degree. value) and the proportion of the dose adsorbed by the lymphatic route. Drugs with Rm.degree. values >10 are absorbed preferentially by the lymphatics (>50% of dose), whereas compds. with Rm.degree. values <4 are hardly absorbed at all by the lymphatics (<10% of dose). By applying the ***prodrug*** principle it was demonstrated that it is also possible to target drugs with Rm.degree. values <4 to the lymphatics. Furthermore, the anal. of the collected lymph samples by ***gel*** filtration, quasi-elastic light scattering, and electron microscopy revealed that, following s.c. administration, mixed micelles are converted into homogeneous, unilamellar vesicles. Mixed micelles may represent a suitable delivery system for low-mol.-wt. drugs whose targets are lymphoid cells. In addnl, for drugs where liposomal application leads to a therapeutic advantage, the thermodynamically stable mixed micelle could be a good alternative to be liposome. However, for both applications a high drug-lipophilicity is a prerequisite.

L7 ANSWER 41 OF 66 CAPLUS COPYRIGHT 2001 ACS

1991:614636 Document No. 115:214636 Chemiadsorbates of p-hydroxybenzoic acid methyl ester on silica as a new type of ***prodrug*** . Part 2. Hydrolysis of chemiadsorbates in acidic aqueous solution and their stability on storage. Srcic, Stane; Rupprecht, Herbert (Fac. Nat. Sci., Univ. Ljubljana, Ljublajana, 61000, Yugoslavia). Eur. J. Pharm. Biopharm., 37(2), 101-5 (English) 1991. CODEN: EJPBEL.

AB The hydrolysis of chemiadsorbates of Me p-hydroxybenzoate (I) on porous and nonporous SiO2 (KG 100 silica ***gel*** and Aerosil OX50, resp.) in 0.01 N HCl at pH 2 in a USP XXII paddle app. did not confirm to pseudo 1st order kinetics, since the desorption curves revealed an initial fast release followed by a prolonged sustained-release pattern. This was particularly pronounced for the nonporous carrier. Studies with I physisorbed on carrier showed the pore structure of marginal importance. Temp. (4-40.degree.) pos. influenced the speed of hydrolysis (no kinetic data). Stability studies showed I on the porous support more stable to hydrolysis at 20.degree. (55% humidity) than than on the nonporous carrier; when suspended in liq. paraffin the drug-carrier system was not hydrolyzed.

L7 ANSWER 42 OF 66 CAPLUS COPYRIGHT 2001 ACS

1991:589591 Document No. 115:189591 Chemiadsorbates of p-hydroxybenzoic acid methyl ester on silica as a new type of ***prodrug*** . III. Modeling and simulation of drug release from chemiadsorbates to acid aqueous solution. Srcic, S.; Rupprecht, H.; Mrhar, A.; Karba, R. (Fac. Nat. Sci. Technol., Univ. Ljubljana, Ljubljana, 6100, Yugoslavia). Int. J. Pharm., 73(3), 221-9 (English) 1991. CODEN: IJPHDE. ISSN: 0378-5173.

AB The in vitro release of physi- and chemiadsorbates of p-hydroxybenzoic acid Me ester (PHBAME) on a colloidal (Aerosil 0 .times. 50; BET surface 50 m2 g-1) and a porous silica support (KG 100; mean pore size 10 nm, BET surface 300 m2 g-1) in an acidic dissoln. fluid was investigated and the release kinetics described by math. modeling with an analog-hybrid computer. The release from physiadsorbates on both the colloidal and the porous silica proved to be a fast process, best described by two release consts. The release from the chemiadsorbates, however, is based on different mechanisms: from the plain surface of colloidal silica (fractal dimension 2.0) the drug release can be best described by two hydrolysis reaction rates while four different reaction rates were evaluated for the release of PHBAME from the porous support. From the reaction rates and the activation energies it is concluded that the hydrolysis of the surface link between the PHBAME and the silica surface, the .scharw.Si-O-C.rscharw. bond is strongly influenced by the surface character of the supports, described by their different fractal dimensions (porous support fractal dimension 2.56).

L7 ANSWER 51 OF 66 CAPLUS COPYRIGHT 2001 ACS

1989:160327 Document No. 110:160327 Immobilized drugs: phenol and benzoic acid derivatives chemiadsorbed on silica. I. Preparation of chemiadsorbates. Eckert-Lill, Christiane; Lill, Norbert; Endres, Werner; Rupprecht, Herbert (Dep. Pharm., Univ. Regensburg, Regensburg, Fed. Rep. Ger.). Acta Pharm. Jugosl., 38(4), 373-9 (English) 1988. CODEN: APJUA8. ISSN: 0001-6667.

AB The chemiadsorption of phenol, benzoic acid and hydroxybenzoic acid isomers on a porous silica support (mean pore diam. 10 nm) via .tplbond.SiOC.tplbond. bonds was studied with a view to developing ***prodrug*** forms. The silica support was activated prior to the drug adsorption by annealing or by the introduction of .tplbond.SiCl bonds. The yield of the chemiadsorption was dependent on the reaction conditions and both the reactivity of the OH group and the structure of the drug mols. The chemiadsorption yield of phenolic compds., contg. the CO2H group is considerably smaller than that of phenol and substituted phenols with alkyl entities (i.e. carvacrol).

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=> E BABICH J/AU
=> S E3,E6,E7,E9

             4 "BABICH J"/AU
            17 "BABICH J W"/AU
            14 "BABICH JOHN"/AU
            58 "BABICH JOHN W"/AU
L9          93 ("BABICH J"/AU OR "BABICH J W"/AU OR "BABICH JOHN"/AU OR "BABICH
               JOHN W"/AU)

=> E ZUBIETA/AU
=> S E6,E12-E16
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            30 "ZUBIETA J"/AU
           471 "ZUBIETA JON"/AU
            56 "ZUBIETA JON A"/AU
             1 "ZUBIETA JON K"/AU
            11 "ZUBIETA JON KAR"/AU
             1 "ZUBIETA JONH"/AU
L10        570 ("ZUBIETA J"/AU OR "ZUBIETA JON"/AU OR "ZUBIETA JON A"/AU OR
               "ZUBIETA JON K"/AU OR "ZUBIETA JON KAR"/AU OR "ZUBIETA JONH"/AU)

=> E BONAVIA/AU
=> S E7-E10

             2 "BONAVIA G H"/AU
             6 "BONAVIA GRANT"/AU
             3 "BONAVIA GRANT H"/AU
             1 "BONAVIA GRANT HOWARD"/AU
L11         12 ("BONAVIA G H"/AU OR "BONAVIA GRANT"/AU OR "BONAVIA GRANT H"/AU
               OR "BONAVIA GRANT HOWARD"/AU)

=> S L9,L10,L11

L12        642 (L9 OR L10 OR L11)

=> S L12 AND L1

L13          0 L12 AND L1

=> S L12 AND L4

L14          4 L12 AND L4

=> D 1-4 CBIB ABS


L14  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2001 ACS
2000:573694   Document No. 133:182988  Organosilicate sol-  ***gel***
     matrixes for drug delivery.    ***Babich, John W.***  ;   ***Bonavia,***
  ***     Grant***  ;   ***Zubieta, Jon***   (Biostream, Inc., USA).  PCT Int. Appl.
     WO 2000047236 A1 20000817, 133 pp.  DESIGNATED STATES: W:  AE, AL, AM, AT,
     AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES,
     FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
     LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
     RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
     ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG,
     CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR,
     NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2000-US3754 20000214.  PRIORITY: US 1999-PV119828 19990212.
AB   Biocompatible matrixes such as sol-gels encapsulating a reaction center
     may be administered to a subject for conversion of prodrugs into biol.
     active agents.  In certain embodiments, the biocompatible matrixes of the
     present invention are sol-gels.  In one embodiment, the enzyme L-amino
     acid decarboxylase is encapsulated and implanted in the brain to convert
     L-dopa to dopamine for treatment of Parkinson's disease.  The silica sol
     was prepd. by the addn. of substituted trimethoxysilanes, tetra-Me
     orthosilicate (TMOS) and 4 mM HCl soln.  Total desired vol. of the sol was
     detd. by the no. of matrixes to be prepd.  Entrapment of penicillinase in
     the matrix was performed by using pH 6.5 phosphate buffer.  The
     penicillinase activity was detd. by using 3 mM soln. of penicillin G in
     buffer.

L14  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2001 ACS
1995:205780   Document No. 122:176882  Synthesis, Spectroscopy, and Structural
     Characterization of Six-Coordinate Bis(aryldiazenido)rhenium and
     Bis(diarylhydrazido)rhenium Complexes. X-ray Structures of
     (Et4N)[Re(NNPh)2(O2C6H4)2], (Et4N)[Re(NNPh2)2(O2C6H4)2], and
     Na[Re(NNPh)2(O2C6H4)2].cntdot.CH3CN.  Kettler, Peter B.; Chang, Yuan-Da;
       ***Zubieta, Jon***   (Department of Chemistry, Syracuse University,
     Syracuse, NY, 13244, USA).  Inorg. Chem., 33(25), 5864-71 (English) 1994.
     CODEN: INOCAJ.  ISSN: 0020-1669.
AB   The reactions of the cis-dioxorhenium(VII)-catecholate complex
     [(CH3CH2)4N][ReO2(O2C6H4)2] (1) with either monosubstituted
     organohydrazines (C6H5NHNH2; 4-BrC6H4NHNH2) or 1,1-disubstituted
     organohydrazines (Ph2NNH2) yield the cis-bis(diazenido) core complexes
     [(CH3CH2)4N][Re(NNR)2(O2C6H4)2] (5, R = C6H5; 6, R = 4-BrC6H4) and the
     cis-bis(hydrazido) core species [(CH3CH2)4N][Re(NNPh2)2(O2C36H4)2] (7).
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Elution of 5 in a 3:1 mixt. of toluene/methanol on a column of silica ***gel*** resulted in cation exchange to give Na[Re(NNPh)2(O2C6H4)2].cntdot.CH3CN (8) as a one-dimensional polymer {[Na(CH3CN)]+[Re(NNPh)2(O2C6H4)2]-}2. Crystal data for C32H38N5O4Re (5): P21/c, a = 14.458(3) .ANG., b = 10.436(2) .ANG., c = 21.767(4) .ANG., .beta. = 107.04(3).degree., V = 3140(2) .ANG.3, Z = 4, R = 0.053. Crystal data for C44H48N5O4Re (7): P1, a = 11.660(2) .ANG., b = 11.864(2) .ANG., c = 15.400(2) .ANG., .alpha. = 107.12(3), .beta. = 94.99(3).permill., .gamma. = 97.61(3).degree., V = 2000(1) .ANG.3, Z = 2, R = 0.0534. Crystal data for C26H18N5NaO4Re (8): P2/n, a = 5.785(1) .ANG., b = 9.670)2) .ANG., c = 23.142(5) .ANG., .beta. = 90.91(3).degree., V = 1294.4(7) .ANG.3, Z = 2, R = 0.049.

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS

1994:157570 Document No. 120:157570 Cleavage of tubulin by vanadate ion. Correia, John J.; Lipscomb, Lewis D.; Dabrowiak, James C.; Isern, Nancy; ***Zubieta, Jon*** (Med. Cen., Univ. Mississippi, Jackson, MS, 39216, USA). Arch. Biochem. Biophys., 309(1), 94-104 (English) 1994. CODEN: ABBIA4. ISSN: 0003-9861.

AB Vanadate is known to cleave proteins in a near-uv-dependent manner. The authors have found that vanadate will cleave .alpha.- and .beta.-tubulin upon photoirradn. (419 nm emission max.) under conditions when tetravanadate, pentavanadate, and decavanadate are in soln. The reaction is independent of GTPMg or GDPMg, and cleavage occurs at two or more sites per chain. Cleavage was studied at pH 6.0 [2-(N-morpholino)ethanesulfonic acid (Mes) and phosphate], Ph 6.9 [piperazine-N,N'-bis(2-ethanesulfonic acid) (Pipes)], pH 7.0 (phosphate), and pH 8.0 [N-(2-hydroxyethyl)piperazine-N'-bis(2-ethanesulfonic acid) (Hepes) and phosphate]. The concn. of vanadate oligomer species, as detd. by 51V NMR, was correlated with the extent of cutting. In org. buffers, low pH and high vanadate concn. favored oligomer formation, esp. tetra and decavanadate. In phosphate buffer at pH 7 and 8, decamer is more prevalent, and at pH 6, phosphate buffer appears to favor a different oligomer form, V', appearing at -582 ppm. Cleavage is best correlated with the presence of cyclic tetravanadate at pH 6.9 in Pipes buffer and the V' species at pH 6.0 in phosphate buffer. Cleavage efficiency is also affected by interactions of photoactivated vanadate species with org. buffer components. In phosphate buffer no photochem. degrdn. of vanadate species occurs. Anal. using sodium dodecyl sulfate (SDS) ***gel*** electrophoresis and western blotting showed that vanadate produced cleavage patterns and nonenzymic cleavage patterns resulting from boiling tubulin in SDS sample buffer (J. J. Correia, L. D. Lipscomb, and S. Lobert, 1993) are not the same. Attempts to identify the locations of the vanadate cleavage sites on the protein through N-terminal sequencing was unsuccessful, apparently due to the presence of blocked amino groups. The authors conclude that tetravanadate cleaves tubulin upon photoirradn., that org. buffers can interact with vanadate oligomers upon photoirradn., and that in phosphate buffer photocleavage is enhanced by an absence of photochem. degrdn. and a preference for forming photoactive vanadate oligomers. These results have general application to photoirradn. studies of any protein in the presence of vanadate.

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS

1993:120045 Document No. 118:120045 c-erbB2 protein overexpression in breast cancer as a target for PET using iodine-124-labeled monoclonal antibodies. Adel Bakir, M.; Eccles, Suzanne A.; ***Babich, John W.*** ; Aftab, Nighat; Styles, Jennifer M.; Dean, Christopher J.; Ott, Robert J. (Jt. Dep. Phys., Inst. Cancer Res., Sutton/Surrey, SM2 5NG, UK). J. Nucl. Med., 33(12), 2154-60 (English) 1992. CODEN: JNMEAQ. ISSN: 0161-5505.

AB ICR 12, one of a panel of rat monoclonal antibodies recognizing the external domain of the human c-erbB2 protooncogene product was chosen as a candidate for radiolabeling with 124I for positron emission tomog. of selected patients with breast cancer. By using N-bromosuccinimide (NBS), optimal labeling conditions were established using 125I. The labeling efficiency was detd. using instant thin-layer chromatog. (ITLC) and ***gel*** filtration (HPLC). The antibody was then labeled with the positron emitter 124I, and a labeling efficiency of 96% and immunoreactivity of 80-90% was obtained. The product was stable, with <5% of the radiolabel being eluted after 6 days storage in plasma at 37.degree.. Immunolocalization studies were performed in athymic mice bearing human breast carcinoma xenografts overexpressing the c-erb B2 gene product using as controls 125I-labeled isotype-matched rat antibody, and antigen-neg. tumors. Good uptake of 124I-labeled ICR12 was obtained in c-erb B2 expressing tumors (up to 12% injected dose per g at intervals up to 120 h), with localization indexes of 3.4-6.2. Tumor xenografts of 6 mm

diam. were successfully imaged with high resoln. at 24, 48, and 120 h using the RMH/ICR MUP-PET camera. It is suggested that 124I-labeled ICR12 is a suitable agent to image and quantify immunolocalization in patients whose tumors overexpress the c-erbB2 protooncogene product.

FILE 'MEDLINE' ENTERED AT 10:29:03 ON 20 APR 2001

=> S PRODRUG;S ENZYME;S GEL

L15 2903 PRODRUG

L16 451666 ENZYME

L17 234038 GEL

=> S L15 AND L17

L18 34 L15 AND L17

=> S SOL(W)GEL

1808 SOL
234038 GEL
L19 204 SOL(W)GEL

=> S L15 AND L19

L20 0 L15 AND L19

=> D L18 1-34 TI

=> S SILICA

L21 10223 SILICA

=> S L15 AND L21

L22 7 L15 AND L21

=> S L22 NOT L18

L23 4 L22 NOT L18

=> D L22 1-7 CBIB ABS

L22 ANSWER 1 OF 7 MEDLINE
2000292106 Document Number: 20292106. Intensely cytotoxic anthracycline prodrugs: galactosides. Bakina E; Farquhar D. (Department of Clinical Investigation, The University of Texas MD Anderson Cancer Center, Houston 77030, USA.) ANTI-CANCER DRUG DESIGN, (1999 Dec) 14 (6) 507-15. Journal code: AC5. ISSN: 0266-9536. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have reported the synthesis of a series of anthracycline analog prodrugs that give rise to intensely cytotoxic metabolites in the presence of carboxylate esterases and beta-glucuronidases. We now report structurally related prodrugs that are converted to similar potent metabolites in the presence of beta-galactosidases. The prototypical compound, N-[(4"RS)-4"-ethoxy-4"(1'"-O-beta-D-galactopyranosyl)butyl]daunorubicin, 8a, was prepared by reductive condensation of daunomycin with 1-O-[(1'RS)-1'-ethoxy-4'-oxobutyl]-2, 3, 4, 6-tetra-O-acetyl-beta-D-galactopyranoside in the presence of sodium cyanoborohydride, followed by deacetylation of the galactoside moiety with sodium methoxide. A related ***prodrug*** (8b) with enhanced lipophilicity (the 4'-hexoxy analog of 8a) and 8c (the propyldaunomycin analog of 8a) were prepared for comparative studies. 8a and 8b were isolated after chromatography on ***silica*** as a mixture of 4'R and 4'S diastereomers; 8c, on the other hand, was resolved into its component 3' diastereomers, 8c(R) and 8c(S). 8a, 8c(R) and 8c(S) showed no evidence of decomposition when incubated at 37 degrees C in 0.05 M phosphate buffer, pH 7.4, for 2 weeks; 8b, under the same conditions, was degraded with a half-life of 49 h. In the presence of two units of Escherichia coli beta-galactosidase per pmol of substrate, the half-lives of 8a, 8b, 8c(R)

and 8c(S) were 1.98, 1.06, 3.5 and 2.4 h, respectively. HPLC analysis of the incubation mixtures showed that 8a and 8b gave rise to a single, chromatographically identical metabolite. 8c(R) and 8c(S) also gave rise to a single, identical metabolite. 8a and 8b were nearly one million-fold more toxic to human A375 melanoma cells in culture in the presence of E. coli beta-galactosidase than in the absence of the enzyme. The activation products of 8c(R) and 8c(S) were approximately 1000-fold less potent. These beta-galactoside prodrugs have chemotherapeutic potential for use in conjunction with tissue-targeting strategies such as antibody-directed enzyme ***prodrug*** therapy (ADEPT) and gene-directed enzyme ***prodrug*** therapy (GDEPT).

L22 ANSWER 2 OF 7 MEDLINE

92392704 Document Number: 92392704. A monoclonal antibody-beta-glucuronidase conjugate as activator of the ***prodrug*** epirubicin-glucuronide for specific treatment of cancer. Haisma H J; Boven E; van Muijen M; de Jong J; van der Vijgh W J; Pinedo H M. (Department of Medical Oncology, Free University Hospital, Amsterdam, The Netherlands.) BRITISH JOURNAL OF CANCER, (1992 Sep) 66 (3) 474-8. Journal code: AV4. ISSN: 0007-0920. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The anti-pan carcinoma monoclonal antibody (MAb) 323/A3, linked to E. coli-derived beta-glucuronidase (GUS) was used to study the tumour-site-selective activation of the ***prodrug*** Epirubicin-glucuronide (Epi-glu). Epi-glu was isolated from the urine of patients treated with Epirubicin (Epi) by reversed phase chromatography on a ***silica*** -C18 column. Epi-glu was stable in human blood and was not converted into Epi by A2780, MCF-7, or OVCAR-3 cancer cells, despite the presence of intracellular GUS. The stability of the ***prodrug*** was confirmed in BALB/c mice. MAb 323/A3 and GUS were linked through a stable thioether bond. The conjugate (1:1) was purified by ion exchange and gel filtration chromatography. Binding to target cells revealed an immunoreactivity of at least 60% and good retention of enzyme activity. A protein dye (sulforhodamine B) assay was used to analyse cytotoxicity. Epi (IC50 of 0.003-0.2 microM) was 100-1,000 times more toxic than Epi-glu (IC50 of greater than 20 microM), when cancer cells were exposed for 4 or 24 h to the drugs. The low cytotoxicity of Epi-glu was most likely due to the reduced cellular uptake rate of the ***prodrug*** (2.7 pmol 10(-6) cells min-1) as compared to that of the parent compound (25 pmol 10(-6) cells min-1). Pretreatment of antigen-positive cells with the 323/A3-GUS conjugate prior to ***prodrug*** exposure completely restored cytotoxicity as a result from hydrolysis of Epi-glu into Epi. Our results demonstrate that the 323/A3-GUS conjugate can specifically activate the stable non-toxic ***prodrug*** Epi-glu at the tumour cell level.

L22 ANSWER 3 OF 7 MEDLINE

90062353 Document Number: 90062353. Quantification of L-3-(3-hydroxy-4-pivaloyloxyphenyl)alanine (NB-355) by high-performance liquid chromatography using o-phthalaldehyde/N-acetyl-L-cysteine derivatization. Hisaka A; Kasamatsu S; Takenaga N; Ohtawa M. (Central Research Laboratories, Banyu Pharmaceutical Co., Ltd, Tokyo, Japan..) JOURNAL OF CHROMATOGRAPHY, (1989 Sep 29) 494 183-9. Journal code: HQF. ISSN: 0021-9673. Pub. country: Netherlands. Language: English.

AB A new and rapid high-performance liquid chromatographic assay has been developed for the determination of L-3-(3-hydroxy-4-pivaloyloxyphenyl)alanine (NB-355,I), a novel ***prodrug*** of L-DOPA. The method involves precolumn derivatization of the drug in biological samples with o-phthalaldehyde (OPA) and N-acetyl-L-cysteine (NAC) in a triethanolamine buffer (pH 8.0), giving a fluorescent compound that is stable for 2 h at 4 degrees C. Use of an internal standard improved the assay in accuracy and reliability. A programmable injector allowed automatic derivatization of large numbers of samples. Chromatographic separation was performed on a reversed-phase column (Capcell Pak C18) in which the ***silica*** gel was coated with silicone polymer. The peaks corresponding to compound I and the internal standard were eluted within 16 min with a mobile phase of acetonitrile-phosphate buffer (pH 7.1). The reliable limit of quantification was 0.5 pmol per injection (0.05 micrograms equivalents of L-DOPA per ml in plasma). The method was successfully applied for the measurements of dog plasma concentrations after oral dosing of compound I.

L22 ANSWER 4 OF 7 MEDLINE

89214552 Document Number: 89214552. Determination of N-n-propylnorapomorphine in serum and brain tissue by gas chromatography-negative ion chemical ionization mass spectrometry. Trainor T M; Vouros P; Lampen P; Neumeyer J L; Baldessarini R J; Kula N S. (Barnett Institute,

Northeastern University, Boston, MA 02115.) JOURNAL OF CHROMATOGRAPHY, (1988 Dec 21) 457 257-66. Journal code: HQF. ISSN: 0021-9673. Pub. country: Netherlands. Language: English.

AB A method for the determination of the neuroactive compound N-n-propylnorapomorphine (NPA) in biological tissues is described. Isolation of NPA from serum or brain tissue was achieved via liquid-liquid extraction from phosphate-buffered tissue extract (0.25 M, pH 7.2) into ethyl acetate. The NPA, along with a [2H7]NPA analogue serving as internal standard, was converted to the corresponding bis(trifluoroacetyl) ester by treatment with excess trifluoroacetic anhydride at 75 degrees C. The electrophoric derivatives were analyzed by fused- ***silica*** capillary gas chromatography-mass spectrometry in the negative ion chemical ionization mode. Selected ion monitoring of the [M-CF3CO]- ions of derivatized NPA (m/z 390) and internal standard [2H7]NPA (m/z 397) permitted the quantitation of NPA in serum and brain samples obtained from rats treated with either free NPA or the ***prodrug*** methylenedioxy-NPA (MDO-NPA). Calibration was conducted down to a practical limit of assay sensitivity, at 0.50 ng NPA per ml of serum and 0.50 ng NPA per g of brain. The relative standard deviation for replicate serum samples spiked at 20 ng/ml was 4.2% (n = 5) and for brain samples at 10 ng/g, it was 3.6%. This method revealed differences in the free NPA brain/serum ratios in rats treated separately with the stereoisomers R-(-)-MDO-NPA and S-(+)-MDO-NPA.

L22 ANSWER 5 OF 7 MEDLINE

89008728 Document Number: 89008728. Simultaneous determination of the ***prodrug*** zofenopril and its active drug in plasma by capillary gas chromatography-mass-selective detection. Jemal M; Ivashkiv E; Teitz D; Cohen A I. (Squibb Institute for Medical Research, Analytical Research and Development Department, New Brunswick, NJ 08903..) JOURNAL OF CHROMATOGRAPHY, (1988 Jun 24) 428 (1) 81-92. Journal code: HQF. ISSN: 0021-9673. Pub. country: Netherlands. Language: English.

AB After oral administration of zofenopril, the active sulfhydryl angiotensin-converting enzyme inhibitor is released. Zofenopril is currently under clinical investigation as an antihypertensive. Blood samples are reacted with N-ethylmaleimide, immediately after collection, processed into plasma and stored frozen for subsequent analysis. After addition of two internal reference standards, one each for the ***prodrug*** and the active compound, the plasma samples are purified by a combination of liquid-liquid and solid-phase extractions. The dried methylated extracts are reconstituted with tetramethylbenzene and chromatographed by automated splitless injection on a fused- ***silica*** capillary column, connected to a mass-selective detector. The analytes and the internal reference standards are chromatographically resolved and a common fragment ion is monitored for the analytes. A limit of quantitation of approximately 1 ng/ml of plasma is achieved.

L22 ANSWER 6 OF 7 MEDLINE

84162469 Document Number: 84162469. Analysis of cortisol, methylprednisolone, and methylprednisolone hemisuccinate. Absence of effects of troleandomycin on ester hydrolysis. Ebling W F; Szefler S J; Jusko W J. JOURNAL OF CHROMATOGRAPHY, (1984 Feb 10) 305 (2) 271-80. Journal code: HQF. ISSN: 0021-9673. Pub. country: Netherlands. Language: English.

AB A sensitive, selective, and reproducible high-performance liquid chromatographic assay for the simultaneous measurement of cortisol and methylprednisolone using dexamethasone as the internal standard is presented. Samples are extracted with methylene chloride, washed with sodium hydroxide and then water, and chromatographed on a microparticle ***silica*** gel column with ultraviolet detection at 254 nm. Sensitivity is greater than 10 ng/ml and the intra-day coefficient of variation is less than 5% for both steroids. The use of porcine liver esterase allows the quantitation of the hemisuccinate ester of methylprednisolone. This assay has been applied in pharmacokinetic studies including investigations of troleandomycin--methylprednisolone interactions. A typical plasma concentration--time profile for methylprednisolone and its ester ***prodrug*** is presented for one subject before and after receiving troleandomycin therapy. Although methylprednisolone elimination is reduced in the presence of troleandomycin therapy, there is no effect on the pharmacokinetics of methylprednisolone sodium succinate.

L22 ANSWER 7 OF 7 MEDLINE

83059220 Document Number: 83059220. Determination of bacmecillinam, an amdinocillin ***prodrug*** , in human and canine whole blood by

reversed-phase liquid chromatography. Westerlund D; Pettersson B; Carlqvist J. JOURNAL OF PHARMACEUTICAL SCIENCES, (1982 Oct) 71 (10) 1148-51. Journal code: JO7. ISSN: 0022-3549. Pub. country: United States. Language: English.

AB Bacmecillinam is an amdinocillin ***prodrug*** designed to be easily hydrolyzed in biological materials, so special procedures were developed for the collection of blood specimens. Whole blood was collected in tubes containing bacampicillin as an adsorption inhibitor and kept at -70 degrees; the extracting solvent, hexane-methylene chloride (9:1, v/v), was added to the cold tubes, and the extraction was performed during the thawing of the samples. The organic phase was partially evaporated before a reextraction to a small volume of acidic aqueous phase was made. The separation was performed on a microparticulate. C18-alkyl bonded ***silica*** packed in glass-lined stainless steel columns. Mobile phase was a buffer (pH 6)-acetonitrile mixture containing N-hexyl-N-methylamine as an adsorption inhibitor. The detection limit was 600 pg/ml of whole blood, and the within-run precision (srel%) was approximately 8% at the 5-ng/ml level.

	L #	Hits	Search Text	DBs
1	L1	3654	PRODRUG	USPAT
2	L2	197984	GEL	USPAT
3	L3	5904	SOL ADJ GEL	USPAT
4	L4	2810	L1 AND L2	USPAT
5	L5	7	L3 AND L1	USPAT